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Add-on treatment with pyridoxine and sulthiame in 12 infants with West syndrome: an open clinical study

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To investigate the effect of sulthiame (STM) in West syndrome (WS) an open, uncontrolled add-on study was undertaken during initial pyridoxine (PDX) therapy in 12 infants, two with idiopathic and ten with symptomatic WS. All patients were initially treated with PDX (150–300 mg kg^{-1} body weight day^{-1}). In seven patients (58%) seizures and hypsarrhythmia stopped during the week after introduction of STM (10 mg kg^{-1} body weight day^{-1}). In one the positive effect was temporary. Five of the responders (42%) remained seizure-free and without hypsarrhythmia under STM monotherapy, while one developed complex partial seizures after 25 months. STM was most effective in idiopathic WS (2/2). During treatment with STM medication no patient suffered side effects attributable to the substance. Further controlled studies are necessary to evaluate the benefit of this potentially effective treatment.

Key words: West syndrome; sulthiame; pyridoxine; add-on therapy.

INTRODUCTION

As the basic mechanisms of epileptogenesis in West syndrome (WS) are still unclear, treatment is mainly empirically based, and an internationally accepted gold standard is lacking. Since the first report on the efficacy of ACTH in 1950[1] many controlled studies with ACTH or steroids have confirmed the still unrivalled benefit of this therapy, recording initial responder rates of up to 90% for ACTH[2]. However, high relapse rates of 35 to 50%[3] and a substantially elevated therapy associated morbidity and mortality curtail the initial therapeutic benefit[4].

Valproic acid is reported to control spasms in 65% of cases within three months[5]. Similar effects in 48–60% of cases were reported for topiramate[6] or vigabatrin[7,8]. Following reports on a beneficial effect of high doses of pyridoxal phosphate in up to 40% of cryptogenic and 10% of symptomatic WS cases[9,10] an initial 1–2 week course of pyridoxine (PDX) has become established in some European countries and Japan.

Until now the sulphonamide derivative and carboanhydrase inhibitor sulthiame (STM), which is used to treat benign partial epilepsies, has not been trialed in WS.

To test whether the hypothesis of STM being effective in WS might justify a controlled study, we added STM openly to our standard initial PDX therapy in children with newly diagnosed WS.

METHODS

Twelve boys aged 4–12 months with newly diagnosed WS (two idiopathic, ten symptomatic, Table 1) were enrolled in the study with informed parental consent. Five of those with symptomatic WS had chromosomal abnormalities, two had been born prematurely, one had fetal alcohol syndrome, one showed cerebral dysgenesis, and one had porencephaly.

One infant suffering from Down syndrome, porencephaly and focal seizures (no. 9, Table 1) developed WS whilst undertaking antiepileptic therapy with phenobarbitone; which was stopped at the commencement of PDX therapy. None of the others had received antiepileptic drugs (AEDs) before developing WS.

All patients received orally administered baseline PDX therapy (300 mg kg^{-1} body weight day^{-1} divided into six doses). This was reduced to 150 mg kg^{-1} body weight day^{-1} or administered intravenously

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Table 1: Anamnestic and therapeutic data of 12 patients with West syndrome.

Patient	Sex	Previous history MRI scan	Onset of West syndrome (months)	Successful treatment	Ineffective substances	Follow-up (months)	Course with ref. to seizures
1	m	Focal neonatal seizures, left hemispheric dysgenesis	4	STM, PDX LTG	PB, VGB	35	Seizure free for 24 mo, then CPS[c]
2	m	Thrombasthenia Glanzmann, fetal alcohol syndrome, micro-cephaly, global brain atrophy	9	STM	PDX	28	Seizure free for 28 mo
3	m	Recurrent pneumo-thorax, MRI normal	8	STM	PDX	29	Seizure free for 29 mo
4	m	Down syndrome, AV septal defect, mitral valve replacement	12	DEX	STM	23	Seizure free for 21 mo
5	m	46, XY, +inv dup (15) no abnormalities in MRI	9	(STM, PDX)[b] VGB	CLB	21	CPS and focal motor seizures
6	m	Preterm 32 weeks GA, esophageal atresia, 46, XY, transl/del. (5p–1p)	8 (6)[a]	VPA	PDX, STM, VGB, CLB, PB	24	Rare grand mal seizures
7	m	Preterm 27 weeks GA, IVH I-II, hydrocephalus, right occipital defect	10 (7)[a]	VGB	PDX, STM, PB	20	CPS
8	m	Down syndrome	16	ACTH, LTG	PDX, STM, CLB,VGB	19	Seizure free for 17 mo
9	m	Down syndrome, right porencephaly	5		PDX, STM, PB, VGB, ACTH, VPA	22	Secondary generalized seizures
10	m	No abnormality	4	STM	VGB, VPA	18	Seizure free for 18 mo
11	m	Left porencephaly, right temporal atrophy	8	STM	PDX	9	Seizure free for 9 mo
12	m	Preterm 30 weeks GA, IVH II-III, enlarged ventricular spaces, cerebral atrophy	9 (7)[a]	STM	PDX	6	Seizure free for 6 mo

[a] conception adjusted age; [b] temporarily effective; [c] CPS = complex partial seizures; GA = gestational age; IVH = intraventricular hemorrhage; STM = sulthiame; PDX = pyridoxine; LTG = lamotrigine; DEX = dexamethasone; VGB = vigabatrin; VPA = valproate; ACTH = adrenocorticotrophic hormone; PB = phenobarbitone; CLB = clobazame.

if gastrointestinal side effects interfered with PDX absorption. After three to four days of PDX alone, STM was added in a dose of 5 mg kg^{-1} body weight day^{-1}. If this had no significant effect on spasms or hypsarrhythmia, the dose was increased to 10 mg kg^{-1} body weight day^{-1}. Patients were reviewed before the introduction of STM, on the day of dose escalation, and three days after high dose treatment with STM. EEG monitoring (including a period of sleep) was performed at each of these stages. Patients were classified as responders if infantile spasms had stopped *and* the EEG showed no hypsarrhythmia; however, the EEG tracing could still contain focal or multifocal epileptic discharges.

RESULTS

None of the patients responded to the initial phase of PDX monotherapy.

Six patients showed a permanent response, with two (nos. 3 and 12, Table 1) becoming seizure-free after the introduction of low doses of STM, but with hypsarrhythmia ceasing only with an increased STM dosage. In the other four patients (nos. 2, 10, 11 and 12, Table 1) both spasms and hypsarrhythmia ceased during the high-dose STM phase. In one briefly responding patient (no. 5, Table 1), the effect did not outlast the increase of STM dosage.

The STM responders included the two children with idiopathic WS but none of the symptomatic patients with chromosomal abnormalities.

In all the responding infants the PDX medication was phased out over a period of 4–6 weeks; neither infantile spasms nor hypsarrhythmia recurred thereafter.

The follow up period lasted from 6 to 35 months in the responding patients. One patient (no. 1) remained seizure-free for 25 months before developing complex partial seizures which responded to phenytoin. The

other five patients successfully treated with STM had no relapse to WS nor did they develop other kinds of seizures. Two of them (nos. 2 and 3) are medication-free after 28 and 29 months respectively.

DISCUSSION

Although its major antiepileptic mechanisms are unclear, the sulphonamide derivative and carboanhydrase inhibitor, STM, may act by lowering the extracellular concentration of $K^{\oplus}$ and pH, leading to a decrease of neuronal excitability[11]. Its anticonvulsant properties are used mainly in the treatment of benign partial epilepsies, as reported in a recent double blind placebo controlled multicenter study[12]. Until now, however, this drug has not been used in the treatment of WS. In view of the good tolerability of STM[13] and its quick onset of action, this open pilot study was initiated for patients with newly diagnosed WS who, with one exception, had received no previous AED.

50% of the treated patients (6/12) exhibited a positive response regarding spasms and hypsarrhythmia throughout the follow up period of up to 35 months. A possible synergistic effect of STM and PDX cannot be proven with this approach but appears unlikely in view of the lasting effect in the responders despite the early withdrawal of PDX. As reported for ACTH and other AEDs in previous studies[14], patients with idiopathic WS responded best (2/2). Infants with chromosomal abnormalities had no benefit from this medication, reflecting the poorer prognosis in symptomatic WS.

Neither the design of the study nor the numbers of patients enrolled allow statistical conclusions to be drawn about the effect of STM. Comparison of the results of this observation with historical data of initial PDX monotherapy suggests that the antiepileptic properties of STM in WS may exceed those of PDX. Further controlled studies are needed to confirm this hypothesis.

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